NEW YORK HEART ASSOCIATION

PART I—ABSTRACT OF PAPERS PRESENTED AT THE SCIENTIFIC SESSION ON RESEARCH, HELD AT THE NEW YORK ACADEMY OF MEDICINE, MAY 7, 1964

*Ischemic Myocardial Metabolism**

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An experiment was designed to examine the extraction and metabolism of palmitate-l-C^{14} by the normal and ischemic myocardium. In the hemodynamic steady state, the cannulated left coronary artery of the dog was perfused with fully oxygenated blood containing palmitate-l-C^{14}. Arterial and coronary sinus (CS) samples were analyzed for O_2, CO_2, glucose, lactate, pyruvate, lipid C^{14}, $C^{14}O_2$ and *p*H. Extracts of serum and left ventricular (LV) myocardium were counted directly and counts fractionated on silicic acid plates. In the experimental group, ischemia was produced by reducing flow to a new steady state. In this group there was an increase in O_2 extraction, decrease in qO_2 and Tension Time Index (TTI), atrial hypertension, a fall in CS *p*H and a 93 per cent increase in CS lactate ("excess" lactate) at a fixed arterial lactate and pyruvate concentration. Palmitate C^{14} extraction increased 97 per cent with decreased flow rates. Although total consumption and retention of C^{14} label was little changed by ischemia, a shift in fractional distribution occurred with a significant increase in the per cent triglyceride. Despite a fall in qO_2 and TTI, palmitate-l-C^{14} consumption remained fixed at preischemic levels. When similar studies of ischemic carbohydrate metabolism were performed, glucose extraction coefficient increased 404 per cent. In contrast to palmitate studies, glucose *consumption* increased 92 per cent despite a 32 per cent fall in TTI. It is postulated that under ischemic conditions, increase in α-glycerophosphate concentration permits a proportionate increase in NEFA esterification and storage as tryglyceride. During ischemia, carbohydrate catabolism may continue, via glycolytic routes, with an increase in glucose consumption and α-glycerophosphate production. A small, but perhaps significant amount of ATP may be produced. There is no lipid counterpart for energy-yielding anaerobic processes and storage may provide the only available pathway for extracted lipid.

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*Inhibition of Exchange Diffusion and Active Transport of Cardiac Potassium by Different Concentrations of Ouabain**

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Intracellular K^+ transport in the working heart *in vitro* occurs at two rates with the more rapidly exchanging process markedly sensitive to temperature ($Q_{10}>2$) and anoxia, suggesting an active transport, but insensitive to ouabain (0.5 mg./l.); and a more slowly exchanging fraction, inhibited by this level of ouabain and insensitive to temperature variation, suggestive of exchange diffusion. The present report concerns studies further delineating these two K^+ transport processes. Guinea pig ventricle slices (400 μ thick) were equilibrated with oxygenated mammalian Ringer's solution (pH 7.4) with K^{42}. At 37° and 25° C., cardiac K^+ content was constant and equilibrated with K^{42} at a single rate (T ½ 60 min.). Despite the apparent single rate of K^+ exchange in control slices, the effects of ouabain indicated two processes. During the first hour of exposure of ventricle slices to ouabain (0.5 or 1.0 mg./l.), K^+ loss occurred which was followed by a constant K^+ content for 3 hours (mean 15.5 mEq./kg.). During this latter period, 90 per cent of the remaining potassium exchanged at a uniform rate three times faster than in the ouabain-free controls. At least part of this remaining K^+ fraction was oxygen dependent since K^+ transfer in either direction was limited in an atmosphere of nitrogen. When the concentration of ouabain was increased to 2, 10, or 20 mg./l., there was no further K^+ loss (mean 15.7 mEq./kg.), but here, the remaining K exchange was limited as seen with anoxia. The data indicate that ouabain at 0.5 mg./l. inhibits one transport system maximally, resulting in K^+ loss only during the first 60 minutes of exposure. The saturation effect is supported by the finding that increasing the concentrations of ouabain resulted in no further K loss. The exchange of the remaining fraction of K^+ is dependent on oxidative metabolism and is inhibited by ouabain only at higher concentrations (> 2 mg./l.). However, this latter inhibition is not associated with further decreases in cellular K^+ and suggests binding of some K^+ to intracellular sites or inhibition of transport in both directions. It is postulated that lower concentrations of ouabain inhibit a transport mediated by a physical rate limiting step, as exchange diffusion, but do not interfere with active transport. The latter is impaired only at higher concentrations of the glycoside.

* This work was supported by a grant from the New York Heart Association, Inc.

*A Plastic Auxiliary Ventricle Permanently Implanted in the Chest**

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Patients suffering from myocardial insufficiency from whatever cause may require continuous intracorporeal assistance. We have therefore developed for experimental use a small plastic air-powered pump for permanent implantation between the ascending and descending aorta. With this device, aortic pressure in dogs dropped during systole and rose during diastole, lowering the left ventricle's resistance toward emptying and reducing its work by as much as 60 per cent. Coronary flow was markedly increased. Contraction of the Silastic bulb in the pump is controlled by an electronically powered solenoid valve triggered by the ECG through a timing device during diastole. The pre-set parameters are not changed during the experiment. In patency studies, a nonfunctioning auxiliary ventricle was implanted in the aorta at different sites. Three dogs with this prosthesis in the abdominal aorta are alive and well up to 19 months postoperatively. In system experiments, the pump has functioned continuously up to 41 hours in conscious dogs without adversely affecting the animals' appetite, physical movement, or sleep. During 41 hours the free serum hemoglobin did not exceed 85 mg. per cent. During 10-hour daily operations for periods up to two weeks, the free serum hemoglobin was usually under 35 mg. per cent. Renal function was unchanged. Pericarditis in one dog improved with pumping, as shown by change in the T wave of the ECG from negative to positive. The pump and its power supply can be mounted on a specially designed harness. Efforts are now being concentrated on developing a similar pump for eventual clinical use in the treatment of chronic myocardial insufficiency.

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*A Rapid Determination of Pacemaking Defects in Patients with Artificial Pacemakers**

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Pacing the ventricles by artificial stimulation is a standard method of treatment for complete heart block. Pacemaking failure is not a rare occurrence. The most common causes have been: 1) malposition of transvenous pacemaker catheters, 2) internal and external wire breaks, 3) short circuits in the core of transvenous pacemaker catheters, 4) failure of the power supply.

The purpose of this report is: 1) to describe a simple method of localizing defects in malfunctioning pacemaking systems with use of the standard electrocardiogram machine, and 2) to demonstrate the characteristic intracardiac electrographic patterns

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obtained from patients in heart block and in normals.

Unipolar electrograms were recorded on the V lead of the electrocardiogram and bipolar electrograms from between the pacemaker electrodes were recorded on lead 1. In the pacemaker patients the electrograms were recorded during idioventricular rhythm. Catheter electrode malpositions were identified by demonstrating extraventricular electrograms, atrial, or extracardiac in character. In instances of wire breaks, no record could be obtained from the compromised electrode. Short circuits between bipolar electrodes produced identical tracings from each of the poles. A bipolar electrogram from between these electrodes could not be obtained and a straight line was recorded. Sustained pacemaker activity was demonstrated by concurrently recording the pacemaker impulse and a standard electrocardiographic lead. Tracings typical of each situation were made.

*Factors Influencing Patterns of Left Ventricular Contraction**

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The use of mercury-filled Whitney gauges sewn to the epicardial surface of the heart permits the measurement of instantaneous length changes in the underlying myocardium of both acute and chronic animal preparations. By this technique it has been shown by others and confirmed by us that the circumferentially oriented fibers lengthen during the isovolumic phase of ventricular systole while the longitudinally oriented fibers shorten. Ejection is accomplished mainly by shortening of the circumferentially arranged fibers.

In order to study the length changes of the isovolumic period in more detail, a balloon was inserted into the left ventricle through an apical stab wound while the animal was on total cardiac bypass. Fluid was added to the balloon in stepwise increments. It was possible, by increasing ventricular volume from 20 to over 40 ml., to cause gauges that had been shortening to lengthen, and gauges that had been lengthening to shorten.

The volume dependence of these ventricular contractile patterns was studied further in the intact dog with chronically implanted gauges. Rapid hemorrhage of up to 40 per cent of the estimated blood volume, as well as sudden increases in circulating volume, resulted in alterations of the control pattern similar to those observed under totally isovolumic conditions. These occurred even when there was little or no change in the time-course of left ventricular pressure. Electrodes placed at various points along the ventricular surface have given evidence that the inhomogeneous contractile pattern is not related to the sequence of electrical activation.

The most likely explanation for this inhomogeneous contractile pattern and its volume dependence is that myocardial fibers at different locations are under different degrees of stretch and that local length-tension relationships result in variations in contractile force. The ability of sympathetic nerve stimulation to modify the basic pattern at a given volume further supports this hypothesis.

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**New York Heart Association Research Trainee.

*Beneficial Effect of Interatrial Shunt in Left Ventricular Failure**

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Although a rise in left atrial pressure in the failing left ventricle will increase ventricular output at first, this mechanism has a limit beyond which further increments in left atrial pressure do not affect ventricular output, but result only in pulmonary congestion. Since left atrial pressure is ultimately generated by the right ventricle, it seemed possible to prevent the right ventricle from developing this useless, indeed harmful excess of left atrial pressure by enabling the right ventricle to pump against a lower resistance. An atrial septal defect provides such a lower resistance.

Left ventricular failure was created in eight dogs by aortic constriction. A left-to-right shunt of known flow was made by pumping blood at a controlled rate from the left atrium to the right atrium. Pressures were measured in both atria, in the aorta on both sides of the constriction, and in the pulmonary artery. Systemic flow was measured with an electromagnetic flowmeter.

Left atrial pressure fell abruptly when the shunt was opened, and it returned promptly to control level when the shunt was closed. The fall in left atrial pressure was proportional to the size of the shunt and to the initial height of left atrial pressure. When shunt flow was 55 ml./min./kg., left atrial pressure fell 32 per cent from 17.8 mm. Hg to 12.1 mm. Hg. Systemic flow declined only 5.3 per cent and right atrial pressure did not rise more than 1 mm. Hg.

This demonstrates that an interatrial shunt can lower left atrial pressure in left ventricular failure without deleterious effects on systemic flow or right ventricular function. It is suggested that a small atrial septal defect made by catheter puncture might provide a self-regulatory *safety valve* for the patient in chronic left ventricular failure unresponsive to traditional measures.

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*Oxygen Uptake by Cat Heart Muscles During Rest and Activity, In Vitro**

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The oxygen uptake of isolated cat papillary muscles and trabeculae carnae was measured at rest and during activity using a form of polarography adapted to a flow microrespirometer. For quiescent muscles the following results were obtained:

1) The inverse relationship between muscle diameter and resting oxygen uptake, reported by Cranefield and Greenspan in 1960, was confirmed. However, in the present study no plateau of QO_2 in the low-diameter range of the diameter-uptake curve was found. The highest average oxygen uptakes determined were 4.31 and 4.93

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**Initial experiments were performed in the Department of Physiology, State University of New York, Downstate Medical Center, Booklyn, N. Y.

μl./mg. wet weight/hr. at 30°C. and 35°C., respectively, for muscles in the diameter range of 0.20 to 0.25 mm.

2) Evidence was obtained showing that as determinants of resting QO_2, changes in resting length or tension are less important than changes in diameter.

3) The assumption that QO_2 is not dependent on PO_2 in isolated heart muscles was evaluated by noting the effects of different ambient oxygen concentrations on resting uptake. The results demonstrate that as the PO_2 reaches some critical level (8 μl./cc.) the resting QO_2 is depressed.

Studies of the rate of oxygen uptake associated with activity again demonstrated the important influence of diameter on oxygen uptake. Using strontium in equimolar amounts as a substitute for calcium, the duration of the isometric twitch was varied while maintaining a constant peak contractile tension. Evidence was obtained which indicated a direct relationship between the total tension developed per cross-section of muscle per unit time (Tension Time Index) and the activity QO_2 in the isometrically contracting muscle.

PART II—ABSTRACTS OF PAPERS SUBMITTED FOR PRESENTATION

*Long-Term Electrophrenic Stimulation in Dogs**

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The phrenic nerve in dogs has been stimulated for periods up to five months, at which point the experiment was terminated because of mechanical failure of the electrodes. The most satisfactory of several electrode designs was of Teflon-coated multistrand, stainless-steel wire with a short Silastic cuff. It could be placed around the nerve with minimal dissection and no interruption of the blood supply. The lead wires were exteriorized between the scapulae, and attached to a portable stimulator mounted, with a separate battery pack, on the harness. Parameters of the stimulus were 0.3 or 0.5 msec. pulse duration, 60-90 cycles/sec. frequency, and 0.15-0.9 volt amplitude. Stimulus trains lasting 0.8-2.0 sec. were repeated at 18-42/min. Bipolar stimulation (two electrodes 1.0-1.5 cm. apart on the nerve) and unipolar stimulation (one electrode on the nerve and the indifferent electrode elsewhere in the body) provoked equally effective contractions of the ipsilateral diaphragm. At least once daily the contractions were checked by palpation of the lower chest and upper abdomen, and the threshold of the stimulus was checked by oscilloscope. The ipsilateral diaphragm moved vigorously throughout the chronic studies. However, when the stimulus was momentarily interrupted after the studies were well under way, diaphragmatic excursions during spontaneous respiration were markedly diminished while the contralateral side moved normally. The reason for this "suppressive effect" is not yet clear. A stimulus of 0.2 volt at the start of chronic stimulation usually rose to about 0.4 volt within 2½ months. The effects were gauged by the end-organ response, as revealed by pneumography, spirometry, fluoroscopy. and cinefluorography. An implantable device, similar to a cardiac pacemaker, is under development for electrophrenic respiration.

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*Homotransplantation of the Heart in Puppies Under Profound Hypothermia**

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The literature reveals a few reports of successful orthotopic homotransplantation of the heart in dogs, but only a small percentage survived because of technical difficulties. Heart homotransplants have been carried out in puppies in our laboratory, with hypothermia but no pump-oxygenator. In an effort to develop a technique ensuring longer survival, the recipient was kept under deep ether anesthesia with profound hypothermia (15°-17°C.). The donor was kept under mild hypothermia (29°-30°C.). The removed heart was immediately placed in cold Tyrode solution. Employing a modification of the technique of Lower and Shumway, we excised and sutured the heart in about 45 min. Normal body temperature was rapidly restored by immersion and by flushing the chest cavity with saline at 42°C. The heart was massaged until the contractions were vigorous and rhythmic, usually 20-30 min. Effective circulation was thus established within 70-80 min., which preliminary studies had shown to be within the safety limit at this temperature. Of 15 dogs undergoing transplants, one survived 20 days. Death was due to pleurisy and possibly the onset of rejection. Four lived more than 24 hours. Histologic studies revealed no sign of myocardial damage or the rejection phenomenon in these animals. Of the remaining 10 dogs, 7 survived more than 10 hours. Only one died of hemorrhage. Deaths were due principally to failure of the heart graft or atelectasis. Immunosuppressive therapy—Imuran and prednisolone combined with thymectomy—will be used in future experiments. A 16-mm. color sound film of the operative technique was made.

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*Pulmonary Blood Flow in the Dog**

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Studies of the pulmonary circulation in the past have been hampered by inability to make direct flow measurements or to vary pulmonary artery flow or pressure. Impaired pulmonary blood flow is the major problem in certain of the congenital cardiac anomalies, and surgical correction may involve dramatic alteration in the pulmonary arterial pressure. We have developed a preparation in which pulmonary artery pressure or flow can be varied at will and measured directly, using a bypass technique

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that allows open- or closed-chest studies. We have attempted to determine specifically the lowest pulmonary artery pressure compatible with pulmonary blood flow adequate to sustain life. This has application in evaluating systemic venous to pulmonary artery shunting procedures.

Measurements were obtained in three dogs with the chest open on positive pressure and in two dogs with the chest closed and breathing spontaneously. Aortic pressure correlated directly with pulmonary artery flow. Pulmonary artery flow at a given pressure varied with the resistance in the circuit. Resistance was higher with the chest open. Above 13 mm. of mercury, adequate flow could be maintained if resistance remained low.

It appears from these studies that the principal factor influencing pulmonary artery flow at a given pressure is the peripheral resistance. Factors that increase resistance are positive pressure breathing, left heart failure, and possibly vasomotor function. Studies are projected to demonstrate which of these factors is the most important.

*Study of the Value of a Vasopressor Agent in the Diagnosis of Carditis in Patients with Acute Rheumatic Fever**

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Difficulty is frequently encountered in the diagnosis of carditis in patients with acute rheumatic fever and an apical systolic murmur. This investigation was designed to establish the value of neosynephrine as a diagnostic aid in questionable cases of carditis. To the best of our knowledge this is the first report of the use of a vasopressor agent for this purpose. We believe that an apical pansystolic murmur is pathological and is valid evidence of carditis in a patient with a first attack of acute rheumatic fever or if the murmur reappeared during a recurrence following its disappearance after a previous attack of rheumatic fever. Ten patients with acute rheumatic fever were studied. Neosynephrine 0.09 mg./kg. was administered subcutaneously following a baseline phonocardiogram. Brachial blood pressures were recorded by the cuff method and the phonocardiogram was repeated at the height of the pressor response. The results were as follows: in three patients questionable apical pansystolic murmurs became definitely pansystolic. One had a pansystolic murmur during the acute phase that waned during convalescence. The murmur was recalled by this procedure. In three patients with pansystolic murmurs the murmurs became much louder. In three patients with what were believed to be innocent murmurs no pathological murmur could be elicited. In one patient a questionable soft high-pitched early aortic diastolic murmur was unmasked. This study demonstrates the usefulness of vasopressor agents in the diagnosis of doubtful cases of carditis.

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**New York Heart Association Trainee.

*The Contractile Response of Pial Arteries to Topical $BaCl_2$ and the Inhibition of Their Response by Other Agents**

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Cerebral vessels are relatively unresponsive to most humoral and neural stimuli that profoundly affect other vascular beds. A method is needed for causing marked local constriction of pial arteries. The response would provide an easily measured end point representing the contractile potential of these vessels. We could then test the ability of many experimental variables to alter this potential by examining their capacity to alter the magnitude of constriction.

$BaCl_2$ (0.5 per cent or 5.0 per cent) caused marked, reversible, reproducible, and atraumatic constriction of pial arteries when topically applied in anesthetized mice. The pia, exposed by craniotomy, was continuously bathed by a flowing irrigation fluid that further dilutes these and all other topically applied solutions. The effects of $BaCl_2$ were not mimicked by solutions of Ca, Mg, Sr, Zn, or Pb with similar *p*H, tonicity, or molarity.

Lead dilated pial arteries and inhibited the response to $BaCl_2$. It was effective in topical concentrations of 10^{-3} *M* or less. These data contradict theories pertaining to lead encephalopathy which ascribe symptoms to a hypothesized ability of lead to constrict cerebral arteries.

Reserpine and phenothiazines also inhibited the response to $BaCl_2$. These results were only achieved with local application of the drugs. In mice tranquilized by systemic administration of these agents the contractile response to $BaCl_2$ was unaltered. Although these data demonstrate, for the first time, an effect of tranquilizers on cerebral blood vessels, they do not support the suggestion of some workers that cerebro-vascular effects may be related to the behavioral effects of these drugs.

Finally, we found that topical nylidrin HCl (Arlidin) inhibited the response to $BaCl_2$ while producing little or no vasodilation. This agent increases the cerebral blood flow in rabbits and some groups of patients. This suggests that our technique may be of value in screening agents of potential therapeutic value in certain forms of cerebrovascular insufficiency.

The results indicate the ability of our technique to demonstrate an effect on intracranial arteries of agents important in the cause or treatment of human disease. The unique effect of barium is of interest in itself, and the mechanism of barium's action is under investigation.

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